CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
PROPOXUR

Chemical Code # 62, Tolerance # 50021
SB 950 # 013

December 30, 1986
Revised 6/17/87, 10/19/88, 3/1/89, 5/8/89, 2/22/90, 2/21/91, 6/13/91, 10/25/91, 11/01/91, 5/27/93, 11/03/93, 12/05/94, 1/05/95, and 12/05/97

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, possible adverse effect
Chronic toxicity, dog:	No data gap, possible adverse effect
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time*

* There are several neurotoxicity studies, including acceptable rat acute and subchronic studies.

Toxicology one-liners are attached.

In the one-liners below:
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T971205
Present revision by Aldous, Dec. 5, 1997

Note: these pages contain summaries only. Individual worksheets may identify additional effects.

All relevant studies indexed as of 12/03/97 are included in this summary. These include record numbers up to 146086 (Document 50021-262). (Aldous, Dec. 5, 1997)

These pages contain summaries only. Individual worksheets may identify additional effects.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED, RAT

NOTE: Two long-term rat studies have been accepted to fill combined chronic and oncogenicity data requirements. Only the feeding study (Record No. 014175) is likely to be suitable for risk assessment, since the other accepted study (inhalation study, Record No. 120845) did not find definitive evidence of tumor causality, and is more difficult to evaluate for route and quantity of absorption. Taken together, the studies do not provide sufficient evidence to consider there to be a tumor effect on the liver. Bladder tumors are clearly treatment-related in rats, as established by several studies, below. Aldous, 3/11/93.

An ancillary submission (50021-229 120474) presented historical control data on uterine tumors. Since it is not clear whether the six cited studies were "selected" from a much larger pool of reference studies, or whether the six studies presented were the only studies which met selection criteria, it appears premature to re-address the issue of uterine tumors in the primary study (Record No. 014175, Sponsor No. 88501) at this time. Aldous, 3/24/93.

**** 50021-095 014175** "Chronic Toxicological Study with Rats (Feeding Study over 106 Weeks.)" (Bayer AG, 8/20/84, Report No. 12870, Sponsor No. 88501). Propoxur, 99.4%; fed in the diet for 106 weeks to 50/sex/group at 0, 200, 1000 or 5000 ppm to BOR:WISW strain rats; Additional 10/sex/group for interim sacrifice at 1 year; oncogenic NOEL = 200 ppm (bladder papillomas and carcinomas in males and females, carcinomas of the uterus), systemic NOEL = 1000 (body weight depression). The incidence of bladder papillomas was 25/49 for high dose males and 28/48 for females compared with none in the controls. Hyperplasia of the bladder epithelium was noted in the medium and high dose groups (both sexes) at the 1-year and terminal sacrifices. For uterine carcinoma, the incidence was 3/49 in controls and 8/48 in high dose group which is not significant ($p = 0.07$) by Fisher's Exact Test. **Acceptable** with **possible adverse effect** for risk assessment. J. Schreider, 2/21/85.

EPA 1-liner: Minimum (oncogenicity), Supplementary (feeding). Oncogenic NOEL = 200 ppm (bladder papilloma in 1/50 males at 1000 ppm.) At 5000 ppm 25/49 males and 28/48 females had bladder papillomas. At 5000 ppm carcinoma of the bladder in 8/49 males and 5/48 females; females also had an increased incidence of carcinoma of the uterus (8/48 females) as compared with controls (3/49). Systemic NOEL < 200 ppm (there was a statistically significant weight depression during weeks 1-20. NOEL for females = 200 ppm. Effects at 1000 ppm (both sexes): weight depression, increased incidence of urothelial hyperplasia of the bladder, slight increase in neuropathy. At 5000 ppm (both sexes) significant (usually $p < 0.01$) weight depression; less food consumption; increased incidence/degree of neuropathy; more splenic atrophy. 44/49 males, 48/48 females had urothelial hyperplasia of the bladder at termination. Males only showed increased thromboplastin time 24 months. Females at 5000 ppm

consistently had lower mean plasma cholinesterase activity than controls and two lower exposure groups.

50021-134 047933 "Incidence of Spontaneous Tumours from Historical Rat Studies". Historical control data from Mobay, 1975 through 1983. Sponsor no. 88769. (J. Gee, 12/28/86).

50021-134 047934 "Frequencies of Spontaneous Tumours in Wistar W. 70 Rats in Chronic Toxicological Tests". Sponsor no. 90236. 1973 to June, 1976. (J. Gee, 12/28/86).

50021-134 047935 "Frequencies of Spontaneous Tumours in Wistar TNO/W 74 Rats in Chronic Toxicological Tests". Sponsor no. 93095. May, 1975 to July, 1976. (J. Gee, 12/28/86).

50021-106 025222 "Cholinesterase-activity in Plasma and Erythrocytes after 3 and 6 Months of Experimental Treatment." (Bayer, 10/29/81.) Single-page memo with mean values for cholinesterase values with no cholinergic effects reported. Supplement to study # T 4 002 110 - see 14175 above.

50021-229 120474 (ancillary data to rat combined study). Karbe, E., "BOQ 5812315, Two-year feeding study in rats", "Supplement title: Historical data on uterine carcinomas of control rats in two-year feeding studies". 12/15/92 (date of the ancillary data submission). Miles Report No. 88501-1. This report was submitted in response to U.S. EPA's HED Peer Review Committee request for historical control data on uterine carcinoma from studies in the same testing facility as the primary combined study [Mobay Chemical Corp. Study No. 88501, DPR Document No. 50021-095, Record No. 014175]. Start dates of cited studies were 1973 to 1980. The six cited studies have the following conditions in common with the cited study: Strain Wistar TNO/W 70 rats from Winkelmann, Borchen; tests performed at Bayer in Wuppertal; diet of powdered Altromin R, from Altromin Co., Lage, Germany; duration of studies, 24 months. Cited studies had uterine carcinoma incidences of 14.4% to 20.0%. Record 014175 had incidence of 16.7%. It is not clear whether the six cited control studies were the only studies which fit selection criteria, or whether they were chosen for submission because they provided comparable uterine carcinoma incidence to Record No. 014175. C. Aldous, 3/24/93.

****50021-237 120845** Pauluhn, J., "BOQ 5812315 (c. n. Propoxur): Study for chronic inhalation toxicity in the rat", Bayer AG Fachbereich Toxikologie, Wuppertal, 11/16/92. Miles Report No. 103955. Sixty Wistar rats per sex per group were subjected to atmospheres averaging 0, 2.2, 10.4, or 50.5 mg/m^3 propoxur (purity > 99%) for 6.3 hr/day, 5 days/wk in a vehicle of a 1:1 blend of PEG 400 and ethanol (mean PEG 400 concentration of 360 to 410 mg/m^3). Of the 60 rats/sex/group, five/sex were sacrificed at 12, 18, and 25 months: the rest were maintained on treatment for 25 months, then taken off treatment for 5 months before sacrifice. Cholinesterase NOEL = 2.2 mg/m^3 (inhibition of RBC cholinesterase in both sexes, and plasma and brain cholinesterase in males).
General non-neoplasia NOEL = 2.2 mg/m^3 (sinus catarrh in mandibular lymph nodes of females). Plausible propoxur treatment responses from aerosol exposure include lymphocyte infiltration in interstitial cells of lungs (high dose males); cell proliferation in harderian gland (high dose, M & F); and sinus catarrh in mandibular lymph nodes (high dose, M & F). A modest increase in hepatocellular adenomas in high dose males was considered to be a very equivocal evidence of a treatment effect. Small numbers of urinary bladder tumors (papillomas in 4 males, carcinomas in 2 females), which lacked apparent dose-response relationship, were considered to be plausibly treatment-related. These indications of tumor responses are **"possible adverse effects"**. This study is **acceptable** in that there were no serious deficiencies from acceptable

protocols. Due to limitations in ability to assess route and dose, this study is nevertheless less useful for most purposes than the combined study (Miles Report No. 88501, DPR Document No. 50021-095, Record No. 014175). Aldous, 3/24/93.

50021-247 132726 [addendum to combined rat inhalation study, Document No. 50021-237, Record No. 120845]. Report dates: 11/16/92 (original report), and 1/28/94 (the present addendum). The U.S. EPA review of this report identified discrepancies between two summary tables in the report, each relating to tumor incidences. This record clarified the bases for the differences between the tables. The original DPR review had been based upon a table incorporating peer-reviewed pathological examinations of serial sections of selected target tissues into the primary pathologist's diagnoses. No changes are required for the DPR review (see worksheet for this submission). Aldous, 12/05/94.

50021-232 120478 Bomhard, E., "Study of the effect of diet on the pH of the urine of male and female Wistar rats". Bayer AG, Wuppertal, 12/17/92. Miles Report No. 103956. Ten rats/sex were fed one of 4 commercial rodent diets to evaluate changes in urinary pH over a 3-wk period. Diets were Altromin® 1324 (pellets), Ssniff 1/0 (pellets), Kliba 343 (pellets), and Purina 5001 (minipellets). Prior to day 0 of treatment, most rats were fed Altromin® 1324 (pellets), however the Purina group was fed Altromin® 1321 (pulverized feed) during the pretreatment period, because the latter feed more closely resembled the physical characteristics of Purina diet. The Altromin® 1321 (pulverized feed) appeared to lower urinary pH in either sex, based on "day -1" measurements. Urine of rats fed Kliba 343 diet (composed largely of casein, starch, and glucose) was typically more acidic than that of other groups during the 3-wk treatment period. This may be important because diet influences urinary bladder tumor incidence, which in turn may be related to urinary pH. Useful ancillary information. Aldous, 2/23/93.

50021-233 120479 Cohen, S.M., "Evaluation of the urine and urinary bladder of male rats fed propoxur (Baygon®) with or without ammonium chloride". Univ. of Nebraska Medical Center, Omaha, 12/15/92. Miles Report No. 103958. Five male inbred Wistar rats per group were placed for 4 weeks on each of the following diets: control (Altromin 1321), nominal 8000 ppm propoxur, or nominal 8000 ppm propoxur plus 10000 ppm ammonium chloride (which acidifies urine). Urine was examined for types and amounts of crystals formed. Bladders, kidneys, livers, and forestomachs were examined by light microscopy. Bladders were also examined by SEM. Body weight gains were markedly reduced in both propoxur groups (39 to 40 g, vs. 108 g in controls). There were no clinical signs of toxicity. In both propoxur groups, absolute weights of kidneys and livers were reduced, however these organs as well as forestomachs were histologically normal. Urinary bladders of all 5 propoxur-only rats had "simple hyperplasia" of the epithelium (typically mild degree) under light microscopy. Two of 5 propoxur/NH_4Cl rats also had "simple hyperplasia", (mild and focal). Controls were normal. Differences were more marked under SEM. On a scale of 1-5 (normal to most severe), control bladders were all normal; two propoxur-only bladders were grade 3 and three were grade 5; whereas three propoxur/NH_4Cl bladders were grade 2, while the rest were normal. There was no evidence of a treatment effect on necrosis or exfoliation of urothelium. Urine of propoxur/NH_4Cl groups was typically 1 pH unit lower than other groups. There were no differences in quantity or form of urinary crystals. Investigators considered a mitogenic process to be consistent with the data, since there was no evidence of a cell damage/repair mechanism, nor evidence of chronic irritation by microscopic urinary crystals. Useful ancillary information. Aldous, 2/24/93.

50021-234 120480 Cohen, S.M., Sangha, G. K., and Van Goethem, D. L., "Discussion of possible mechanisms for propoxur-induced urinary bladder tumors in the rat". Discussion dated

12/21/92. Miles Report No. 103957. This review of studies to evaluate mechanisms of rat urinary bladder tumors considered studies already reviewed by DPR. Propoxur or a metabolite was postulated to operate on or with growth factors to elicit hyperplasia and eventual tumor development. Since some propoxur metabolites are phenols, and since some phenols share with propoxur the property of being urinary bladder oncogens only at extremely high dose levels, threshold effects may be present. Low urinary pH was noted to inhibit binding of epidermal growth factor, which is abundant in rat urine. This is consistent with rat studies, in which pH reduction markedly reduced the extent of hyperplasia. Perspectives offered in this discussion suggest that propoxur-induced tumors in rats may not be relevant to man, but the "possible adverse effect" designation remains until more definitive evidence can be obtained. Aldous, 2/24/93.

50021-088; 009592, 009594, 009595, 009596, 009597, 009598, 009599, 009601, 009602, 009603, 009604, 009605, 009606, 009607, 009608:
These records contain registrant's statements and additional data related to an adverse effects disclosure found at document # 50021-095, record # 014175. These records were reviewed by R. G. Wang, J. B. Knaak, and P. E. Berteau (see document # 50021-088; letters dated 8/31/84, 8/22/84, 8/16/84). No worksheets were done (S. Morris, 10/6/88).

NOTE: Records 071087 to 071094 below generally represent ancillary studies relevant to rat combined study 095:014175, which found dose-related hyperplasias and neoplasias in urinary bladders of male and female rats. These ancillary studies employed only females, however there is no reason why males should not have been similarly affected. Factors predisposing to bladder hyperplasia and neoplasia development were (1) Species: rats (Sprague-Dawley and Wistar) were affected, but golden hamsters and NMRI mice were not. (2) Diet: In rats, a standard rodent diet (Altromin® 1321) always yielded hyperplasias, as well as neoplasias, in studies of sufficient duration; however "semi-synthetic" casein-based diet did not yield hyperplasias or neoplasias in urinary bladder. The presence or absence of added vitamin C had no bearing on bladder hyperplasia or tumor outcome in rats. (3) Time to effect in rats: hyperplasias began to appear in two to four weeks, and progressed over time and with increasing dose to papillomas and eventually carcinomas. (4) Reversibility: exposure of a few week's duration led to early stages of hyperplasia, which was apparently fully reversible. (5) Reactive metabolite implicated: limited evidence was presented implicating a metabolite, perhaps 2-isopropoxyphenyl hydroxymethylcarbamate (2-IPHMC), as responsible for hyperplasia and neoplasia seen in rats. Rats appear to be less able to further metabolize 2-IPHMC compared to man and other species. In conclusion, these ancillary studies do not permit CDFA to dismiss the rat urinary bladder tumor findings as "not relevant to man", however these studies substantiate the NOEL of the primary combined study, and demonstrate that tumors follow a progression of hyperplastic lesions. There was no apparent bladder neoplasia without advanced hyperplasia, suggesting that protection of persons from chronic toxicity to the bladder should eliminate concerns about neoplasia. C. Aldous, 2/22/89.

50021-166 071087 "Propoxur: Subchronic feeding test on female Wistar rats (Effect of feed quality)". Study # T5019041. Bayer AG Toxicology Division, 7/13/88. 50 female rats [Wistar, Bor strain: WISW (SPF Cpb)] per group, controls and one test group of 8000 ppm propoxur (99.9% purity, identified by synonym, BOQ 5812315, in the report) in diet. Diet was "a semi-synthetic basal diet with no vitamin C supplement". Toxicity at 8000 ppm (approx. 850 mg/kg/day) was demonstrated by a 59-g weight gain decrement over 14 wk. Rats were sacrificed as follows for gross and microscopic examinations of urinary bladders, kidneys, and livers: 4 wk (5 rats/group), 8 wk (5 rats/group), and 14 wk (40 rats/group). There were no

positive histopathological findings. **Acceptable as an ancillary study** to combined study 095:014175. C. Aldous, 2/2/89. (Note: a brief summary of study is in 131:040897)

50021-223 115679 Bomhard, E., and Hahnemann, S., "BOQ 5812315 (Common name: Propoxur), Subchronic feeding study using female Wistar rats (Effect of the simultaneous administration of sodium nitrate on feed quality)", Bayer AG, Fachbereich Toxikologie, Wuppertal, Jan. 2, 1992. Report No. 102683. Propoxur (99.6%), composite batch F1. 133, was administered in diets of 30 female Wistar rats/group. Since possible $NaNO_3$interaction with propoxur was of interest, six treatment combinations were tested, including 0 ppm propoxur with either 0, 50, or 150 ppm $NaNO_3$, and 8000 ppm propoxur with either 0, 50, or 150 ppm $NaNO_3$. Ten rats/group were necropsied at week 4, and the balance at week 13. Substantial and consistent b.w. differences were obtained with propoxur treatment, irrespective of $NaNO_3$ levels (decrement at week 13 was about 60 g). Common gross findings in the urinary bladder in all propoxur groups were dilated blood vessels, and increased consistency (decreased transparency) of the bladder wall. Two cases of mild epithelial hyperplasia of the urinary bladder among 8000 ppm propoxur (without $NaNO_3$) vs. no comparable changes in any other groups was considered a possible treatment effect. There was no other treatment-related histopathology noted. It was concluded that $NaNO_3$ did not accentuate effects of propoxur. Useful data, although study design does not address SB-950 data gaps. **No adverse effects**. Aldous, 11/3/93.

50021-166 071088 "BOQ 5812315 (common name: Propoxur): Chronic feeding test on Syrian gold [sic] hamsters (Species sensitivity)". Study No. T0018434. Bayer AG Toxicology Division, 6/15/88. Hamsters were fed propoxur (99.6 to 99.9% purity, identified by synonym, BOQ 5812315, in the report) in diet. Diet was "a fixed-formula standard diet" (Ssniff H-Mehl). 50/group (female only) at 0, 3000, and 8000 ppm. Scheduled sacrifices per group (No. animals) = 4 wk (5), 9 wk (5), 12 wk (10), 27 wk (10), and 1 yr (20). Body weight gain decrements and clinical signs ("emaciation" and "poor general condition") appear to have been treatment-related findings. There were no positive histopathological findings, and no adverse effects indicated. **Acceptable as an ancillary study** to combined study 095:014175. C. Aldous, 2/3/89.

50021-130 037421 Interim report for 166:071088, above.

50021-174 072492 Re-submission of 166:071088, above. Reports are identical, except for change(s) in cover page(s) to conform to EPA requirements.

50021-166 071089 "BOQ 5812315 (common name: Propoxur): Chronic feeding test on Sprague-Dawley rats (Strain sensitivity)". Bayer AG Toxicology Division, 6/16/88. Study No. T1018435. Propoxur (99.6 to 99.9% purity) in diet. Diet was Altromin® 1321 Mehl. 50/group (female only) at 0, 3000, and 8000 ppm. Scheduled sacrifices per group (No. animals) = 4 wk (5), 9 wk (5), 12 wk (10), 27 wk (10), and 1 yr (20). Body weight gain decrements were statistically significant ($p < 0.01$) in both treatment groups and were dose-related. Hyperplasia of the urinary bladder urothelium was time and dose-related, demonstrating a response in these Sprague-Dawley rats similar to that of Wistar rats fed the same diet in an earlier combined chronic/oncogenicity study 095:014175. **Acceptable as an ancillary study** to combined study 095:014175. C. Aldous, 2/3/89.

50021-175 072493 Re-submission of 166:071089, above. Reports are identical, except for change(s) in cover page(s) to conform to EPA requirements.

50021-130 037422 Interim report for 166:071089, above.

50021-166 071090 "Propoxur: Chronic feeding test on NMRI mice (Species sensitivity)" Bayer AG Toxicology Division, 6/15/88. Study # T9018433. Diet was Altromin® 1321 Mehl. 50/group (female only) at 0, 3000, and 8000 ppm. Scheduled sacrifices per group (No. animals) = 4 wk (5), 9 wk (5), 12 wk (10), 27 wk (10), and 1 yr (20). **No adverse effects indicated:** no hyperplasia in urinary bladder and no other toxicity in urothelium was observed. There was no NOEL observed: (fatty liver at both treatment levels). **Acceptable as an ancillary study** to combined rat study 095:014175. C. Aldous, 2/6/89.

50021-130 037423 Interim report to 166:071090, above.

50021-176 072494 Re-submission of 166:071090, above. Reports are identical, except for change(s) in cover page(s) to conform to EPA requirements.

50021-167 071091 "Propoxur: Chronic feeding test on female rats over 2 years (Dose-effect-time relationship)". Bayer AG Toxicology Division, 8/15/88. Mobay Report No. 90357. Study had several sections, all involving exclusively female rats. The main section involved dosing 70 rats/group with 0, 50, 250, 1000, 3000, 5000, or 8000 ppm in diet (Altromin® 1321 Mehl). These animals were dosed for 4, 7, 12, 26, 53, 78, or 104 weeks prior to gross examination, and microscopic examination of bladders and kidneys for all groups, and ureters and livers from selected groups. Small numbers of additional rats were assigned to recovery studies over the same dosage range. An additional group of fifty 8000 ppm rats was assigned to short term exposure studies (4 to 28 day exposures) or short term exposure/recovery studies. The urinary bladder was the only organ shown to be affected. NOEL was originally placed at 250 ppm (based on statistically significant incidence of mild simple urinary bladder hyperplasia beginning at 53 weeks of treatment at 1000 ppm). The NOEL was changed to 50 ppm (see below). Papillomas were observed at 3000 ppm at 2-year term of study, in association with greater degree and earlier onset of hyperplasia. Trends continued in 5000 and 8000 ppm groups, with papillomas and carcinomas. Tumors were observed as early as 78 weeks in the 8000 ppm group. At least 2 weeks were required to elicit the earliest signs of hyperplasia in the 8000 ppm group. Reversibility was indicated following exposures as long as 4 weeks at 8000 ppm, but only a limited amount of hyperplasia was present to be reversed at this short duration of exposure. **Acceptable as an ancillary study**. Study 50021-230:120475 (below) justifies a change in the NOEL from 250 ppm to 50 ppm, based on mild simple hyperplasia and on a single case of papillary hyperplasia. C. Aldous, 2/10/89 and 3/2/93.

50021-130 037424 Interim report for 167:071091, above.

50021-230 120475 Hahnemann, S. "PROPOXUR: Chronic feeding test on female Wistar rats over 2 years (Dose-effect-time relationship)". Bayer AG, Wuppertal (conducted original study), date (of present report) 12/15/92. Miles Report No. 90357-1. This record provides additional data requested by U.S. EPA for the 1988 study: Record No. 071091, Miles Report No. 90357. U.S. EPA had requested histopathology examinations to be performed on all uteri in the study, because of a possible increase in uterine carcinomas. The examinations were done, and the data did not indicate a uterine tumor effect. U.S. EPA also requested further information about urinary bladder tumor findings: specifically (1) re-cuts of bladder sections should be made, and the new findings should be correlated with gross observations (particularly "increased consistency and/or decreased transparency"), which did not appear to have a NOEL in the

original report, (2) a second pathologist should examine re-cut bladder sections, and compare the new diagnosis with gross findings. In response, a morphometric analysis was performed on bladder sections, and no systematic differences in thickness were found. Also, the original slides were examined by a consulting pathologist, who found them to be of good quality, so that re-cuts would not provide additional useful information. The re-examination of sections confirmed primary findings, and did not identify evidence of bladder wall thickening at lower dose levels. A conservative NOEL of 50 ppm is supportable, based on a slight increase in mild hyperplasia, and on a single case of papillary hyperplasia at 250 ppm (neither of these observations being statistically significant). The original study remains acceptable as an ancillary study, with a change of NOEL from 250 ppm to 50 ppm. Aldous, 3/2/93.

50021-167 071092 "BOQ 5812315 (Common name: Propoxur): Chronic feeding study on female Wistar rats (Effect of feed and drinking water type)". Bayer AG Toxicology Division, 9/13/88. Study No. T 2018436. Semisynthetic diet made of casein, starch, glucose, cellulose, soy oil, vitamins (no vitamin C included), and minerals. Dosages: 0, 3000, and 8000 ppm in diet for 2, 4, 8, 14, 26, or 100 weeks. Females only: 5/group for 2 to 8 week treatments, 10/group for 14 and 26-week treatments, and 15/group for 100 week treatment. No NOEL established: marked dose-related body weight decrements. No adverse effects indicated: in particular, no microscopically evident urinary bladder effects were observed at any dose. **Not acceptable as an ancillary study**, (clinical observations data seemed very improbable, and an explanation for apparent discrepancies between in-life palpable mass observations and gross necropsy data is needed). Possibly upgradeable. C. Aldous, 2/16/89.

50021-130 037425 Interim report of 167:071092, above.

50021-168 071093 "Propoxur: Status of the studies and assessment regarding oncogenic potential to the urinary bladder". (A review, dated 2/1/88, of chronic/subchronic, mutagenicity and metabolism studies). Several arguments were presented which suggested that a metabolite, perhaps 2-isopropoxyphenyl hydroxymethylcarbamate (2-IPHMC), might be the cause of hyperplasia and subsequent neoplasia of urinary bladder urothelium. Evidence that 2-IPHMC might be causative of these tumors, which have been found only in rats, were (1) This was the only rat urinary metabolite of propoxur to be conjugated as a mercapturic acid, suggesting appreciable chemical reactivity, (2) In vitro studies found 2-IPHMC to be the predominant propoxur metabolite in rat liver postmitochondrial fractions, but not in fractions prepared from other species, (3) There is a dietary factor in rat bladder tumor development, and a diet fed to rats which developed propoxur-caused bladder tumors elevated cytochrome p-450-dependent metabolism much more than did a synthetic diet. Rats on the latter diet did not develop bladder tumors, suggesting differential metabolism as a possible reason for different outcomes. (4) Rats are virtually unable to further metabolize 2-IPHMC under in vitro conditions, whereas other species (including man) can further metabolize 2-IPHMC. Information suggests reasons why bladder tumor development due to propoxur may be species-specific to rats and therefore not relevant to human health concerns. C. Aldous, 2/17/89.

50021-168 071094 "Propoxur: Chronic feeding test on female Wistar rats with added 1% L-(+) ascorbic acid", Study # T8018432. Bayer AG, Toxicology Division, Wuppertal, 8/2/88. Only females were tested; doses were 0, 1000, 3000, and 8000 ppm, either with or without 1% ascorbic acid in Altromin® diet. Termination was at or about week 50, with up to 30 rats/treatment scheduled for terminal sacrifice, plus lesser numbers for interim sacrifices. Ten 8000 ppm rats were taken off diet at week 9 and sacrificed 6 wk later in a recovery study. Apparent NOEL = 1000 ppm (body weight decrements and urinary bladder hyperplasia and

occasional papillomas or carcinomas, dose-related and irrespective of dietary ascorbic acid, at 3000 and 8000 ppm). Hyperplasia was seen at 3000 ppm and above beginning at week 4. The limited recovery study found no evidence of hyperplasia, however the degree of hyperplasia which would have been expected at 9 weeks of exposure was very mild, hence the importance of evidence of apparent recovery is questionable. Aldous, 2/22/89.

50021-215 098838 [ancillary study to further evaluate known effect of urinary bladder hyperplasia in rats]. Bomhard, E., Hahnemann, S., and Hartmann, E., "BOQ 5812315 (Common name: Propoxur). Study of the reversibility of changes in the urinary bladder urothelium. (13-Week feeding study with 8-week recovery period using female Wistar rats)." [Mobay Report No. 101902]. Bayer AG, Fachbereich Toxikologie, Wuppertal, Aug. 15, 1990.
Groups of 20 female rats per group were treated with propoxur in diet at 0 or 8000 ppm for 87 days. Additional groups of 20 were given the same propoxur treatment, then taken off treatment for an additional 8 weeks for a recovery study. Urinary bladders, kidneys, and (in the case of the 13-week study only) ureters were examined microscopically. Urinary bladder hyperplasias were noted in 15/20 of the rats treated for 87 days with propoxur: no hyperplasias were seen in controls nor in propoxur rats following 8-wk recovery. Study is **acceptable** as an ancillary study, with some minor deficiencies. Study did not seek nor find a NOEL, nor was an "adverse effect" found. Aldous, 11/1/91.

CHRONIC TOXICITY, RAT

50021-027 017611 "BAY 39007 - Chronic Toxicological Studies on Rats." (Bayer AG, 2/29/68, Report No. 726, Sponsor no. 22991). Propoxur, 99.8%, fed in the diet to 50/sex in control and 25/sex/group at 0, 250, 750, 2000 or 6000 ppm for 2 years; apparent NOEL= 250 ppm (body weight gain, increased liver weight), cholinesterase NOEL not established (no methodology). Initially reviewed as acceptable with variations; re-reviewed as unacceptable (no analysis of diet was performed, no clinical observations, histopathology on only 5/sex/group and limited tissues.) No adverse effect was identified. J. Schreider, 2/20/85 and J. Gee, 6/2/87.

EPA 1-liner: Supplementary (for oncogenicity). Cholinesterase NOEL not established (due to lack of method), systemic NOEL = 250 ppm (increased liver weight.) Pathology reported for only 5 rats/sex/group.

50021-027 017610: Pathology report by Huntingdon Research Centre for record # 017611 (reviewed with record # 017611 by J. Schreider, 2/20/85).

50021-027 017615: One-year interim report of volume # 50021-027, record # 17611.

50021-117 026397: This record contains an exact duplicate of the study found at volume # 50021-027, record # 017615.

50021-120 026408: This record contains an exact duplicate of the study found at volume # 50021-027, record #'s 017610 and 017611.

50021-130 037420 "Chronic longterm toxicity of the carbamate propoxur." Excerpt from doctoral dissertation of A. Jurek, Institute of Medical Technology, Warsaw, Poland, 10/9/77. Propoxur, technical, 97.25%, fed in the diet to 20/sex/group at 0, 50, 200 or 800 mg/kg of food to Wistar rats for 18 months; cholinesterase NOEL = 200 mg/kg food; systemic NOEL > 800 mg/kg

food; unacceptable (no individual data, limited histopathology, no analysis of diet.) No adverse effect reported (J. Gee, 12/27/85).

50021-090 003503: This record contains brief summaries of 2-year feeding studies in rats and dwarf pigs. No adverse effects were indicated in the ranges tested (lower than subsequent studies), hence no written CDFA review.

CHRONIC TOXICITY, DOG (including subchronic dog studies)

**** 50021-098 014192** "BOQ 58 123 15: Chronic Toxicity to Dogs on Oral Administration - (12 Months Feeding Study)". (Bayer AG, 4/11/84, Report No. 12605, Sponsor no. 86665, study T5 001 400). Propoxur, 99.4%; fed to Beagle dogs, 6/sex/group, at 0, 200, 600 or 1800/3600/5400 ppm for 1 year; acceptable with possible adverse effect of hemolytic anemia; NOEL = 200 ppm (increased liver weight, cholinergic symptoms, decreased weight gain, increased cholesterol, blood parameters). J. Schreider, 2/25/85. [Note that the only effect noted at 600 ppm in the 2/25/85 review was "increased relative liver weight". In addition, that review concluded that 1800 ppm would not have elicited sufficient toxic response to properly characterize chronic effects, and that the "adverse effects" became evident only at 3600 ppm and above. Aldous, 10/18/91].

50021-213 098621 Ruf, J. and Mager, H., "BOQ 5812315: Chronic toxicity to dogs (26-Week feeding study)". Bayer AG, Wuppertal, Feb. 5, 1991. Mobay reference No. 101280. Four beagles/sex were assigned to 0 or 70 ppm propoxur (100% a.i.) groups (in diet) for 6 months. No definitive treatment effects were found. **Acceptable as an ancillary study** (relates to 1-yr dog study, 098:014192 or Mobay reference no. 86665). Aldous, 10/25/91.

50021-106 012244 Progress report for 014192.

50021-123 026411: Exact duplicate of # 50021-098, record # 014192.

50021-117 026396 "BOE 5812315 [Baygon]/Chronic Toxicity to Dogs". (Bayer AG, 1/15/82, Sponsor no. 80596.) Propoxur. Table of plasma and cholinesterase values and table of body weights for Study No. T 5001400 - see # 014192. J. R. Gee, 9/10/85.

** 50021-027 017613 "Bay 39007, Chronic Toxicological Studies on Dogs". (Bayer AG, 1/29/68, Report No. 669, Sponsor no. 22814.) Propoxur, 99.8%, fed in the diet to 4/sex/group, Beagle dogs, at 0, 100, 250, 750 or 2000 ppm for two years; probable NOEL = 750 ppm (mortality, body weight decreased gain); no cholinesterase depression (may have been due to methodology); Acceptable (note that no analysis of diet was included in the report.) J. Schreider, 2/19/85.

EPA 1-liner: No CORE grade. Systemic NOEL = 250 ppm (decreased body weight, food consumption; increased liver weight.)

50021-027 017612; "Pathology Report of the Two-year Toxicity in Dogs of Compound BAY 39 007 by Oral Administration;" Huntingdon Research Centre, England, 1/28/69; supplemental to 017613; J. Schreider, 2/19/85.

50021-027 017616: 6-month interim report for 027:017613.

50021-119 026407: Exact duplicate of 027:017613.

50021-264 156561 Technical Grade Propoxur: A Subchronic Toxicity Feeding Study in the Beagle Dog; R. D. Jones and S.G. Lake; Bayer Corporation Agriculture Division, Stilwell, Kansas; Report # 96-176-GT; 8/26/97; 2-(1-Methylethoxy)phenol methylcarbamate (Propoxur) (99.5 - 99.7% , Batch # PT. 234501027); 4 dogs/sex/dose; 0, 60, 600, 1800 ppm (Average daily consumption, M: 0, 2.1, 22.4 and 66.8 mg/kg/day; F: 0, 2.0, 21.1 and 65.8 mg/kg/day) ; No mortalities due to test article were observed. A trend of decreased food consumption and body weight in the 1,800 ppm males was considered to be compound related. Statistically significant increased relative liver weights were observed in the 1800 ppm females. Statistically significant decreased absolute spleen weights were noted in the 600 and 1800 ppm males. Compound related elevated cholesterol levels for both males (600 and 1800 ppm) and females (1800 ppm), decreased albumin levels for both males and females (1800 ppm) and decreased total protein levels for both males and females in the 1800 ppm group. No other significant changes in clinical observations, ophthalmologic, pathological or neurologic observations were observed at any treatment level and considered compound related. NOEL (M) = 60 ppm (M: 2.1 mg/kg/day), (F) = 600 ppm (F: 21.1 mg/kg/day); based on elevated cholesterol, decreased absolute spleen weight). **Acceptable (Miller, 8/16/97)

SUBCHRONIC, MONKEY

50021-139 051526 "Subchronic study of toxicity to rhesus monkey after oral administration by stomach tube for 13 weeks to check for possible findings in the urinary bladder". 3 monkeys/sex at 40 mg/kg/day for 13 wk by gavage in tylose (methylcellulose) suspension. No controls were used. Transient ChE inhibition was observed: up to about 50% inhibition of plasma ChE was measured 1 hour after dosing during weeks 12 and 13. In addition, transient signs, such as excessive salivation, were commonly seen for a few minutes after dosing. There were no other distinctive clinical signs nor blood chemistry nor hematology effects. There were no remarkable gross findings, nor were microscopic signs evident in urinary bladder, nor in other organs examined. **Not acceptable** to fill data gap, but useful information. No CDFA worksheet. C. Aldous, 2/28/89.

ONCOGENICITY, RAT

(See combined, rat section.)

ONCOGENICITY, MOUSE

****50021-228 120110** Bomhard, E., "BOQ 5812315: Study for carcinogenicity in B6C3F1 mice (Twenty-four month feeding study)", Bayer AG, Fachbereich Toxikologie, Wuppertal, 7/27/92. Miles Report No. 103254. Bayer Study No. T 2030315. BOQ 5812315 (propoxur), 99.6%, Batch No. 233896114 = 234801556 was fed in diet to Bor: B6C3F1 (SPF-Han) mice at doses of 0, 500, 2000, or 8000 ppm. Ten mice/sex/dose were allocated to a 1-yr interim sacrifice group, and 50/sex/group were assigned to the 2-yr study. NOEL = 500 ppm [epithelial hyperplasia of urinary bladder (M & F), liver hepatocellular vacuolation (F), increased plasma alanine aminotransferase (ALAT) activity (M & F), increased liver weights at 1 yr (F)]. Increased hepatocellular adenomas were noted in 2000 and 8000 ppm males. Common findings at 8000

ppm included statistically significant body weight gain decrements (M & F); increased HCT and hemoglobin concentrations (M & F); blood chemistry changes of increased ALAT and alkaline phosphatase, decreased inorganic phosphate, protein, and albumin; hemorrhage and thrombus formation in females; and "eosinophilic deposits" in kidneys of males. **Acceptable, with "possible adverse effects"** (especially liver tumors; and secondarily, urinary bladder hyperplasia). Aldous, 2/22/93.

50021-231 120477 Bomhard, E., "Study of the effect of diet on the pH of the urine of male and female B6C3F1 mice". Bayer AG, Wuppertal, 12/17/92. Miles Report No. 103959. As in the corresponding rat study (Document No. 50021-232, Record No. 120478, Miles Report No. 103956), ten animals/sex were fed one of 4 commercial rodent diets to evaluate changes in urinary pH over a 3-wk period. Diets were Altromin® 1324 (pellets), Ssniff 1/0 (pellets), Kliba 343 (pellets), and Purina 5001 (minipellets). Prior to day 0 of treatment, most mice were fed Altromin® 1324 (pellets), however the Purina group was fed Altromin® 1321 (pulverized feed) during the pretreatment period, because the latter feed more closely resembled the physical characteristics of Purina diet. As in the corresponding rat study, Altromin® 1321 (pulverized feed) appeared to lower urinary pH in either sex, based on "day -1" measurements. Urine of female mice fed Kliba 343 diet (composed largely of casein, starch, and glucose) was typically more acidic than that of other groups at day 13 and day 21 (there was no such change in males). Useful ancillary information. Aldous, 2/23/93.

50021-106 012246 "BOE 5812315: [Propoxur, the Active Ingredient of Baygon] Chronic Toxicity Study on Mice (2-Year Feeding Experiment)". (Bayer AG, 5/12/81, Report No. 9954, Sponsor no. 69686.). Propoxur, 99.6%, batch no. 75/40; fed to 50/sex/group CF1/W 74 mice at 0, 700, 2000 or 6000 ppm daily for 2 years; 10/sex/group additional for interim sacrifice; oncogenic NOEL $\geq$ 6000 ppm, systemic NOEL = 2000 ppm (slightly lower body weights in males, some organ weight differences); unacceptable (excessive mortality and tissue autolysis compromised the results, no justification of dose selection, no analysis of diet.) J. Schreider, 2/26/85.

EPA 1-liner: Minimum. Oncogenic NOEL 600[0] ppm (HDT) - typographical error in 1-liner for dose. NOEL = 700 ppm (increase in survival time in both sexes.)

50021-122 026410: Exact duplicate of 106:012246.

REPRODUCTION, RAT

NOTE: Study 50021-202:096549 (Mobay Report No. 100650) is a recent study which was designed, conducted, and reported to reflect current guidelines (see CDFA Medical Toxicology Review of that study). The CDFA review of that report does not indicate a "possible adverse effect". A much older study (50021-029:017609, completed by Bayer AG on 5/13/68 under Report No. 798) was deficient in many ways with respect to modern guidelines, and was classified in a 1985 CDFA Medical Toxicology Branch review as having indicated a "possible adverse effect". Since both reports provided reasonably high LELs and NOELs for general toxicity and reproductive effects, it is not appropriate to continue classifying this study type as indicating a "possible adverse effect". Aldous, 6/13/91.

**50021-202 096549 Suter, P.; Biedermann, K.; Luetkemeier, H.; Chevalier, H. J.; and Terrier, Ch. "BOQ 5812315 (c. n. Propoxur) Two-generation reproduction study in the rat". (Mobay

Report No. 100650). RCC (Research & Consulting Co. AG), Itingen, Switzerland, 12/20/90. Wistar/HAN rats, 25/sex/group, were treated with 0, 100, 500, or 2500 ppm propoxur in diet for 2 generations, one litter/generation. Parental NOEL = 100 ppm (modest body weight and food consumption decrements, and inhibition of brain and RBC cholinesterases at 500 ppm: body weight decrements were more marked in 2500 ppm F1 males and females). Developmental NOEL = 500 ppm (reduced body weight gains in lactating pups (F1 and F2), increased mortality in F2 lactating pups after day 4). Urothelial hyperplasia was noted in 2500 ppm males and females. Originally classified "not acceptable" (needing documentation of stability of test article as administered). Ancillary information in Record 093211, below, provided the requested data. **Acceptable**. **No adverse effects indicated**. Aldous, 6/13/91, 10/25/91.

50021-212 093211 (ancillary information to study 202:096549, above. The original Medical Toxicology Branch review determined that the study could be upgraded if the stability of the test article as prepared for the primary reproduction study could be demonstrated over a period of at least 2 weeks. The present study shows test article in pelleted feed to be stable for up to 21 days at room temperature at nominal concentrations of 200 and 5000 ppm. New data allow an upgrade of the primary study to acceptable status. Aldous, 10/25/91.

50021-239 121835 "Range finding study to the two-generation reproduction study in rats", (P. Suter, K. Biedermann, H. Luetkemeier and Ch. Terrier, RCC, Research & Consulting Co. AG; and RCC, Umweltchemie AG, Project No. 207303, 9/13/91). Miles Report No. 101921. Propoxur, purity 99.3%, admixed with feed at 0, 200, 1000 or 5000 ppm was fed to one generation of 10 Wistar rats/sex/group. Rats were treated from 3 wk premating until after lactation in a single mating trial. An additional 5/sex/group were allocated mainly for cholinesterase (ChE) activity assays. Parental NOEL = 200 ppm/day (reduced food consumption, reduced body weights, reduced RBC ChE activity). Brain ChE activity was also reduced at 5000 ppm. Developmental NOEL = 200 ppm (reduced body weights of lactating pups). There was an indication of a reduction of implantation sites, and of an increase in postimplantation loss at 5000 ppm, based on examinations of uteri of 4-5 dams/treatment. Given the magnitude of the dose, and the large magnitude of effects of that dose on food consumption and body weights in dams, the above uterine observations do not identify "possible adverse effects". There were no findings in this study which would impact major conclusions of the primary study which followed (DPR Record No. 096549; Mobay Report No. 100650). (Kishiyama and Aldous, 5/27/93).

50021-235 120481 "Supplementary Study to the Two-Generation Reproduction Study in the Rat", (A. Dotti, J. Kinder, K. Biedermann, H. Luetkemeier and K. Weber. Portions of study were performed at RCC (Research Consulting Company LTD), RCC Umweltchemie AG, and BRL (Biological Research Laboratories Ltd). RCC Project No. 286997, Miles Report No. 100650-2, 12/2/92). BOQ 5812315 (Propoxur), 99.8 % purity, was administered in the diet at concentrations of 0, 30 or 80 ppm for two generations of 25 Wistar/HAN rats/sex/group. There were no findings in the supplementary study to alter reproductive or parental toxicity NOELs determined from the primary reproduction study above (202:096549). An equivocal decrease in RBC cholinesterase activity in 80 ppm parental F1 males was noted in the present study. This might be a treatment effect, however the lack of clinical signs at doses as high as 2500 ppm in the primary study suggests that cholinesterase changes are not pivotal findings. (Kishiyama and Aldous, 3/4/93).

50021-029 017609 "Bay 39007, Generation Studies on Rats". (Bayer AG, 7/20/73 (revised), initial date 5/13/68, Report No. 798, Sponsor no. 23299). Propoxur, 98.4%, fed to 10 males/20

females per group at 0, 250, 750, 2000 or 6000 ppm; pretreated for 70 days before mating; each female was mated with 3 males during the duration of one cycle (19 - 20 days); mated 2 females to one male at a given time; parental NOEL = 750 ppm (decreased body weight gain), apparent reproductive NOEL = 750 ppm (decreased litter size, decreased lactation index, lower pup weight); unacceptable (no necropsy, no analysis of diet, no clinical observations, mixed mating.) Report contains statement that animals on 2000 and 6000 ppm "displayed normal behavior...." J. Schreider, 2/26/85. NOTE: The 1985 CDFA review had indicated a "possible adverse effect" for this study. That flag has been removed as of 6/13/91, considering the high NOELs and lack of characteristic reproductive effects below 6000 ppm. (Aldous)
EPA 1-liner: No core grade. Reproductive NOEL = 250 ppm (decreased pup number)

50021-121 026409: Exact duplicate of 029:017609.

TERATOGENICITY, RAT

** 50021-179 073509 "Embryotoxicity study (including teratogenicity) with BOQ 5812315 (c. n. Propoxur) in the rat". RCC Umweltchemie AG, 3/1/89. 0, 3, 9, and 27 mg/kg/day (nominal) by gavage to Wistar rats on days 6-15 of gestation. No adverse effects. Maternal toxicity NOEL = 3 mg/kg/day (based on clinical signs which lasted 1-2 hr after dosing). Developmental toxicity NOEL = 27 mg/kg/day (no developmental toxicity). **Acceptable**. C. Aldous, 5/8/89.

50021-028 017619 "Bay 39007 - Examinations for Embryo Toxic Effects Among Rats". (Bayer AG, 11/16/70, Report No. 2388, Sponsor no. 29035). Propoxur, 98.4%, fed in the diet at 0, 1000, 3000 or 10,000 ppm, entire gestation period, 10 females per group; maternal NOEL = 1000 ppm (body weight gain, food consumption), teratogenic NOEL $\geq$ 10,000 ppm, fetotoxic NOEL = 1000 ppm (fetal weight, resorptions). Unacceptable (inadequate numbers of females per group, treatment over entire gestation rather than during organogenesis, no individual body weights, no clinical observations.) J. Schreider, 2/15/85.

EPA 1-liner: No CORE grade. Maternal NOEL = 1000 ppm (body weight and food consumption decreased), Teratogenic NOEL > 10,000 ppm (HDT), Fetotoxic NOEL = 1000 ppm (average weight of fetus significantly lower.)

50021-130 037430: Exact duplicate of volume # 50021-130, record # 017619.

50021-019 017608; "The Classification of Bone Alterations Observed for Rat Fetuses Cleared and Dyed with Alizarin Red S:" This record contains information supplemental to 028:017619 (S. Morris, 10/3/88).

50021-117 024725; "Toxic and Teratogenic Effects of Insecticides in Duck and Chick Embryos"; Study not evaluated.

50021-090 003505: This record contains a brief summary of a 3-generation "teratogenicity" study. This study was not evaluated: it pre-dated the 8/3/73 Technical Bulletin which contained this 2-paragraph summary; the design of the study was vastly different from current guidelines; maximal dosage was lower than 028:017619, above; and "no gross teratologic effects" were identified. No further information needed. C. Aldous, 3/1/89.

TERATOGENICITY, RABBIT

** 50021-179 073510 "Embryotoxicity study (including teratogenicity) with BOQ 5812315 (c. n. Propoxur) in the rabbit". RCC Umweltchemie AG (Itingen, Switzerland), 3/1/89. 0, 3, 10, or 30 mg/kg/day by gavage in 0.5% Cremophor aqueous suspension to Chinchilla rabbits on days 6-18 post coitum. No adverse effect indicated: the limited developmental findings were observed at a clearly maternally toxic dosage. Maternal NOEL = 10 mg/kg/day (transient restlessness and dyspnea following treatment, 3 maternal deaths, and transient reduction of food consumption at 30 mg/kg/day). Developmental NOEL = 10 mg/kg/day [slight increase of abnormally ossified or fused sternebrae (possible treatment effect), and slight ossification delays in some phalanges (more likely to be treatment effects)]. **Acceptable**. C. Aldous, 5/8/89.

50021-106 012245 "BOQ (=BO) 5812315: Evaluation for Embryotoxic and teratogenic Effects after Oral Administration to the Rabbit". (Bayer, 9/9/81, Report No. 10183, Sponsor no. 80034). Propoxur, no purity stated; given by oral gavage to 15/group at 0, 1, 3 or 10 mg/kg, Himalayan CHBB:HM rabbits; days 6 - 18 of gestation; maternal NOEL $\geq$ 10 mg/kg/day, teratogenic NOEL $\geq$ 10 mg/kg/day; unacceptable (inadequate high dose, no purity of test article, no food consumption, no corpora lutea counted.) J. Schreider, 2/26/85.

EPA 1-liner: Minimum. Teratogenic NOEL > 10 mg/kg/day (HDT), maternal NOEL > 10 mg/kg/day (HDT), fetotoxic NOEL > 10 mg/kg/day (HDT).

GENE MUTATION

The data gap is filled for Propoxur by information in records 014184, 014187, 014189, 051524, and 070820. There was no adverse (mutagenic) effect noted from Propoxur even after metabolic activation with rat liver S9 fraction. Supplementary studies with metabolites were also reviewed. A possible adverse effect (weakly mutagenic) was noted in record #014180 from the metabolite THS 1241b in more than 1 trial, but no other positive findings were reported.

Bacteria

50021-019 017607 "Propoxur - Mutagenicity Test on Bacterial Systems". (Nitokuno, Agricultural Chemicals Institute, 2/24/78, Report No. 103, Sponsor no. 65844). Propoxur, 98.0%; tested in Salmonella strains TA1535, TA1537, TA98 and TA100 with phenobarbital-induced rat or mouse liver for activation; tested at 0, 0.1, 10 or 1000 ug/plate with activation, at 1000 ug/plate without activation; sample, S9 and bacterial suspensions spread on the plates with a spreader; single value per concentration per strain; no evidence of a mutagenic effect is reported; unacceptable (no justification of highest concentration, single plate, no repeat trial, no cytotoxicity, minimal protocol). J. Schreider, 2/21/85.

EPA 1-liner: Acceptable. Not a mutagen with and without metabolic activation (S-9 from both rat and mice) in TA1535, TA1537, TA98 and TA100.

50021-098 014191: This record contains an exact duplicate of the study found at volume # 50021-019, record # 017607.

50021-098 035647: This record contains an exact duplicate of the study found at volume # 50021-019, record # 017607.

50021-118 026399: This record contains an exact duplicate of the study found at volume # 50021-019, record # 017607.

50021-113 014184 "Propoxur - Mutagenicity Test on Bacterial Systems". (Institute of Environmental Toxicology, Japan, 8/28/79, sponsor no. 88587.) Propoxur, 98%; Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 as well as Escherichia coli strain WP2 hcr; tested with and without rat liver activation, duplicate plates, one trial; tested at 0, 10, 50, 100, 500, 1000 or 5000 ug/plate; no evidence of increased reversion rate; unacceptable (no repeat trial.) J. Schreider, 2/20/85, and J. Gee, 12/29/86.

50021-098 014187 "Propoxur, Microbial Mutagenicity Study". (Institute of Environmental Toxicology, Japan, Sponsor no. 84124.). Propoxur, 98%; Salmonella strains TA1535, TA1537, TA1538, TA100 and TA98 with and without rat liver activation, also E. coli WP2 hcr strain; tested at 0, 500, 1000, 2500, 5000, 10,000 and 25000 ug/plate in duplicate, one trial; cytotoxic at > 5000 ug/plate in all strains; no evidence for increase in reversion rate. Previous review found data acceptable but noted that only 1 trial was made. For clarification, a second review gives the status as unacceptable for filling a data gap since only 1 trial was made (J. Schreider, 2/25/85 and 6/16/87).

50021-118 026403: This record is an exact duplicate of the study at document # 50021-098, record # 014187.

** 50021-098 014189 "Carbamate UN Technical: Salmonella/Microsome Test to Evaluate for Point Mutation". (Bayer AG, 6/12/82, Report No. 11301, Sponsor no. 82726). Carbamate UN technical, mixture of 5 batches, nos. 100201, 100216, 100222, 10226 and 10034, 98.6%, containing BOQ 5812315; tested with Salmonella strains TA1535, TA1537, TA98 and TA100, with and without rat liver activation; tested at 0, 20, 100, 500, 2500 and 2500 ug/plate, trial 1, and at 0, 750, 1500, 3000, 6000 and 12000 ug/plate, trial 2, four plates per concentration; no evidence of reversion is reported. J. Schreider, 2/25/85.
Acceptable.

50021-118 026401: This record is an exact duplicate of the study at document # 50021-098, Record # 014189.

50021-118 026400; "Mutagenicity Screening of Pesticides in the Microbial System;" Mutation Research, 40:19-30 (1976). Journal article by Shirasu et al. reporting screening on 166 pesticides. Propoxur was considered negative in studies, however insufficient data for meaningful CDFA review. **Unacceptable**: no worksheet. (Aldous, 2/28/89).

50021-118 026406: This record contains an abstract of an article on the mutagenicity of organophosphate insecticides. This record was not relevant and therefore not evaluated.

50021-113 035654 Summary of a series of tests in Salmonella and E. coli including 17606, 14189 and several publications, all negative.

Yeast

** 50021-139 051524 "Test on S. cerevisiae D7 to evaluate for point mutagenic effect". (Bayer AG, Wuppertal-Elberfeld, #13966, 10/30/85). Propoxur (99.8%) in DMSO was added to suspension cultures of S. cerevisiae for 16 hours at 37 C with and without activation at

concentrations of 75-10,000 ug/ml in 3 tests. Aliquots of the suspension were plated on growth and selective agars. Decreased survival was observed at 10,000 ug/ml; no adverse (mutagenic) effect was observed. Acceptable. (Harnois 5/29/87)

Mammalian Cells

** 50021-165 070820 "Propoxur Mutagenicity Study for the Detection of Induced Forward Mutations in the CHO-HGPRT Assay in vitro." (Bayer AG, Germany, Report 98290, 8/31/88) BOQ 5812315, batch 233896114, 99.6%; tested with Chinese hamster ovary cells, CHO-K1-BH_4, with and without male rat liver activation; incubated 5 hours; without activation at 0 (negative and vehicle - DMSO), 25, 50, 75, 100 or 125 μg/ml, duplicate cultures, two trials; with activation at 0 (negative and vehicle), 600, 800, 900, 1000 or 1500 μg/ml, duplicate cultures, two trials; tested to adequate levels of cytotoxicity; **acceptable**. No adverse effect. Gee, 2/23/89.

Propoxur metabolite studies for Gene Mutation

50021-095 014180 "THS 1241b: Salmonella/Microsome Test to Evaluate for Potential Point Mutation". (Bayer AG, 7/9/84, Report No. 12795, Sponsor no. 88510). Propoxur metabolite THS 1241b batch 17101983, no purity stated; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100, with and without liver activation; 0 to 8748 ug/plate, 4 plates per strain and concentration; trial 1: 0, 8, 40 or 200 ug/plate; trial 2: 0, 50, 100, 200, 400 or 800 ug/plate; trial 3 with TA1535 (which showed sporadic doublings of the spontaneous rate): 50, 100, 200, 400 or 800 ug/plate; trial 4 and 5 (all strains): to 5000 ug/plate; additional trials with TA1535 alone to 8748; in almost every trial with TA1535, one or more concentrations with or without S9 activation showed at least a doubling of the spontaneous rate. The actual values, however, are quite low. This is identified as a possible adverse effect for confirmation in other genotoxicity studies and chronic tests. Acceptable for test with a metabolite of Propoxur. J. Schreider, 2/22/85.

50021-095 014177 "Brenzcatechin, Salmonella/Microsome Test to Evaluate for Potential Point Mutation". (Bayer AG, 12/20/83, Report No. 12322, Sponsor no. 88507). Brenzcatechin, batch VK 32-800, possible metabolite of propoxur, no purity stated; tested with Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100 with and without rat liver activation; tested by plate incorporation procedure with 4 plates per concentration at 0, 20, 100, 500, 2500 or 12,500 ug/plate in trial 1 and at 0, 625, 1250, 2500, 5000 or 10,000 ug/plate in trial 2, cytotoxic at > 2500 ug/plate; no increase in reversion rate; acceptable as ancillary study (Note: no purity of test article and use of a metabolite of propoxur.) J. Schreider, 2/22/85.

50021-095 014179 "THS 2490, Salmonella/Microsome Test to Evaluate for Point Mutation". (Bayer AG, 3/6/84, Report No. 12529, Sponsor no. 88509.). THS 2490, metabolite of propoxur, lot no. 3111, no purity stated; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 with and without rat liver activation; four plates per concentration; 0, 312.5, 625, 1250, 2500 or 5000 ug/plate, two trials; no cytostatic effect to 5000 ug/plate; no increase in reversion reported. Acceptable ancillary study (Note: no purity stated and use of a metabolite of Propoxur. J. Schreider, 2/22/85.

50021-095 014181 "Isopropoxyphenol, Salmonella/Microsome Test to Evaluate for Point Mutation". (Bayer AG, 12/20/83, Report No. 12321, Sponsor no. 88581). Isopropoxyphenol, batch VK 32-806, metabolite of propoxur, no purity stated; Salmonella strains TA1535, TA1537, TA98 and TA100, with and without rat liver S9; four plates per strain per concentration; 0, 20,

100, 500, 2500 or 12500 ug/plate in trial 1, 0, 625, 1250, 2500, 5000 or 10,000 ug/plate in trial 2; bacteriostatic at 10,000 ug/plate; no evidence for increased reversion reported; acceptable for metabolite study (no purity stated). J. Schreider, 2/22/85.

50021-130 037426 "THS 1240, Salmonella/Microsome Test to Evaluate for Potential Point Mutation". (Bayer AG, 2/24/84, Report No. 12483, Sponsor no. 90359). THS 1240, batch no. 3112, metabolite of propoxur; tested with Salmonella strains TA 1535, TA1537, TA1538, TA98 and TA100, with and without rat liver activation, 4 plates per concentration per strain, at 0, 312.5, 625, 1250, 2500 or 5000 ug/plate; incomplete with all tables of data (1 - 9) missing so cannot evaluate results. Report states negative results. Upgradeable with submission of missing pages. J. Gee, 12/27/85.

50021-130 037427 "Propoxur Urine Extract compared with Control Urine Extract; Salmonella/Microsome Test to Evaluate for Potential Point Mutation". (Bayer, 3/14/85, Report No. 13350, Sponsor no. 89085). Propoxur; urine from chronic study with rats fed 0 or 8000 ppm; collected 24-hour urine, processed and extracted; tested with Salmonella strains TA1535, TA1537, TA98 and TA100 without activation; 4 plates per sample, 0, 14.5, 29, 58 ul propoxur origin urine - 58 ul equivalent to 1.42 ml urine. Bacteriostatic at highest amount. No indication of mutagenicity. Supplemental information. Unacceptable. J. Gee, 12/27/85.

50021-130 037428 "Propoxur Urine: Salmonella/Microsome Test to Evaluate for Potential Point Mutation". (Bayer AG, 3/27/85, Report No. 13395, Sponsor no. 89086). Propoxur; urine from rats in chronic study fed 8000 ppm was processed and extracted; tested for mutagenicity in Salmonella strains TA1535, TA1537, TA98 and TA100 with and without activation; freeze-dried urine equivalent to 767 ul per plate; no evidence of reversion, slight bacteriostatic effect. Unacceptable for data gap. Supplementary information. J. Gee, 12/27/85.

50021-124 026416; "THS 2647, Salmonella/Microsome Test to Evaluate for Potential Point Mutation;" Mutagenicity study using a metabolite of Propoxur.

CHROMOSOME EFFECTS

SUMMARY: Although there is one report of positive effects on sister chromatid exchange and micronuclei formation [no record number; Cid, M. G. et al., Mutation Research 232: 45-48 (1990)], the weight of evidence is for negative genotoxicity in several other studies. No adverse effect is noted at this time based on the collective data. Gee, 3/23/93.

in vivo

** 50021-130 037429 "Propoxur BOQ 5812315 Sister Chromatid Exchange in the Bone Marrow of the Chinese Hamster in vivo to Evaluate for Harmful Effect on DNA". (Bayer, 5/22/85). Propoxur, 99.6%, batch 234 401 740; given in a single oral dose to 5/sex/group at 0, 14.5, 75 or 150 mg/kg; sacrificed at 24 hours after dosing; dose selection based on pilot test at 10 - 600 mg/kg in which 100 mg/kg was tolerated well; no evidence of induction of sister chromatid exchange in 20 metaphases/animal. Acceptable with minor variances. J. Gee, 12/27/85.

50021-152 064609; "Cytogenetic Study of the Spermatogonia of the Chinese Hamster In Vivo to Evaluate for Harmful Effect on Chromosomes," (Report No. 94310; Bayer AG, Institute of

Toxicology, Wuppertal-Elberfeld, Federal Republic of Germany; 8/20/86) Propoxur, 99.6%, suspended in 0.5% aqueous Cremophor emulsion; 10 male Chinese hamsters/dose were dosed po at 0 and 24 hours with test material at 0, 75, or 150 mg/kg, dosed ip with colcemid (3.3 mg/kg) 5.5 hours before sacrifice at 24 hours; metaphase spermatogonia chromosomes examined microscopically; adequate positive controls; no dose-related clinical abnormalities seen in hamsters; no dose-related cytogenetic abnormalities seen in metaphase chromosomes; no adverse effect indicated; study unacceptable but upgradeable with submission of adequate rationale for doses. S. Morris, 9/23/88.

50021-075 026402 "BOE 5812315 - Dominant Lethal Study on Male Mouse to Test for Mutagenic Effects". (Bayer, 1/7/80, Report No. 8808, Sponsor no. 69368, Study no. BOE 5812315/001). Dominant lethal in mice, propoxur, 99.2%; given by oral gavage in a single dose at 0 or 10 mg/kg to 50 NMRI males per group; mated 1:1 with females for 12 matings of 4-day duration; no evidence of an adverse effect; unacceptable (single dose which caused no toxic effects, no positive concurrent control or acceptable historical positive control data.) J. Schreider, 2/21/85.

EPA 1-liner: Acceptable. No effect on reproduction.

50021-118 026402: Exact duplicate of 075:026402.

50021-028 017618: "Mutagenic Study with Baygon in Albino Mice." Invalid IBT study.

50021-118 026398: Exact duplicate of 028:017618.

50021-098 014190 "BOE 5612315, Micronucleus Test on Mouse to Evaluate BOE 5812315 for Mutagenic potential". (Bayer AG, 6/27/80, Report No. 9274, Sponsor no. 69317). Propoxur, 99.2%; given by oral gavage twice at 5 and 10 mg/kg to 5/sex/group and sacrificed 6 hours after the second dosing; Trenimon as positive control; 1000 polychromatic erythrocytes were scored for micronuclei and the number of normochromatic erythrocytes per 1000 PCE's evaluated; no evidence for genotoxic effect reported; unacceptable (protocol - should be at least a 24 hour sampling as well, no justification of high dose with no toxicity so high dose inadequate.) J. Schreider, 2/25/86.
No EPA 1-liner.

50021-113 035655 Summary of 14190 and a publication in Mutation Res, 1977 - negative.

50021-113 035656: This record contains a summary of a dominant lethal test published in Rocz. Panstw. Zakl. Hig. 28(6):601-613 (1977).

See also Record 071723 under DNA damage below. Gee, 5/8/89.

in vitro

** 50021-173 072053 "Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells." (Microbiological Associates, No. 98464, 12/22/88) Baygon technical, 97.8%, Lot 0030208, tested with CHO cells for chromosome aberrations; without activation at 0 (negative and DMSO), 157, 313, 625 or 1250 μg/ml, 18 hour exposure and 20 hour harvest time; with rat liver activation, at 0, 625, 1250, 2500 or 5000 μg/ml, 2 hour exposure with 10 hour harvest; duplicate cultures per concentration; scored 50 cells per culture and recorded mitotic indices; tested to cytotoxicity; no evidence for an increase in aberrations; **acceptable.** J. Gee, 2/24/89.

50021-200 096032 This document contains a copy of a rebuttal to EPA's evaluation of the study at doc. # 50021-173, rec. # 072053. Evaluation of these data resulted in no change in study status. No worksheet was done (S. Morris, 02/21/91).

50021-139 051525 Sister chromatid exchange in human lymphocyte cultures in vitro to test for DNA modifying effects. (Bayer AG, Wuppertal-Elberfeld, #13871, 10/9/85.) Propoxur (99.6-100%) in DMSO was added to cultures of PHA stimulated human lymphocytes (2 cultures/sex/group) for 2.5 hrs with activation (22.5 hr recovery) at 250, 500, and 1000 ug/ml and for 24 hrs without activation at concentrations of 125, 250 and 500 ug/ml. Cultures harvested by standard procedures; 20 metaphases/cultures reviewed. There was a decreased mitotic index, but no structural aberrations or SCE induced by Propoxur; the positive control, Mitomycin C, failed to induce 2X background levels of SCE in 3/4 cultures without activation and cyclophosphamide failed in 2/4 cultures. The positive controls had no effect on structural aberrations and variable effect on the mitotic index. NOT ACCEPTABLE. Lack of a clear effect by positive controls precludes evaluation for adverse effects from the test substance (Harnois 6/1/87).

No Number "Genotoxicity of the Pesticide Propoxur and Its Nitroso Derivative, NO-Propoxur, on Human Lymphocytes in vitro." (Cid, M. G., D. Lorin and E. Matos, Servicio de Carcinogenesis Quimica y Ambiental, Argentina, Mutation Research 232: 45-48 (1990)) Propoxur and NO-propoxur (no purities stated) were tested with human lymphocytes in whole blood at 0 (DMSO), 50, 100 or 200 μg/ml. Cells were placed in culture with phytohemagglutinin P and bromodeoxyuridine for 24 hours, then exposed to either compound for 48 hours prior to harvest. There were two trials with 50 second-division metaphases scored for sister chromatid exchanges and 2000 interphase cells for micronuclei per concentration. Statistically significant increases in both SCE's and micronuclei were noted with both compounds. **Unacceptable** (no activation included, summary data only) **with a possible adverse effect.** Gee, 2/18/93.

DNA DAMAGE

Note: Report numbered 071723 was categorized as an 844 study type in accordance with FIFRA listing of chromosomal studies as either 843 or 844 - see pages 150 and 151 of Subdivision F, 1984. There were already two reports acceptable under 843 (record numbers 037429 and 072053), both negative. The collective data from the three studies - any one of which could be considered for either test type - are negative for effects of Propoxur on chromosomes or DNA. Gee, 5/8/89.

** 50021-177 071723 "Propoxur - Cytogenetic Studies of the Bone Marrow of the Chinese Hamster in vivo to Test for Harmful Effect on Chromosomes." (Bayer AG, FGR, 9/16/88, Study 98468) Propoxur (BOQ 5812315), two batches >99.5%, tested in Chinese hamsters; given in a single oral gavage dose at 0 (vehicle of 0.5% Cremophor) or 150 mg/kg with 5/sex treated with propoxur sacrificed at 6, 24 or 48 hours and vehicle controls at 24 hours only in test 1; in the second test, doses of 0, 75, 150 or 300 mg/kg were given to 5/sex/group and sacrificed at 48 hours - time based on the first test; a marginal increase in aberrations (excluding gaps) seen at 48 hour with 150 mg/kg was not confirmed at 150 mg or seen at 300 mg (which dose was somewhat toxic); cyclophosphamide as positive control with sacrifice at 24 hours only; **acceptable** with no adverse effect. Note: Considered as a DNA damage/other study based on two adequate studies already existing for chromosomal effects. Gee, 5/8/89. See also next 1-liner. Gee, 10/25/91.

50021-211 093116 "Cytogenetic studies of the bone marrow of the Chinese hamster in vivo to test for harmful effect on chromosomes." (B. Herbold, Bayer AG and Microbiological Associates, 7/2/91, Mobay No. 98468-1) [The study is complementary to 071723 and was conducted at the request of US EPA] BOQ 5812315, 99.4 to 99.8%, was given by oral gavage at 0 (0.5% Cremophor), 75, 150 or 300 mg/kg body weight in a single dose. Sacrifice times were 6 and 24 hours post-treatment with 5/sex at each time. One hundred metaphases were scored per animal (by Microbiological Associates) with a total of 1000 per sacrifice time. Cyclophosphamide was the positive control. There was no evidence of cytogenetic effects. **Acceptable as a supplementary study to 071723.** Gee, 10/24/91.

** 50021-186 074880; "Unscheduled DNA Synthesis in Rat Primary Hepatocytes" (Study No. T8297.380; Microbiological Associates, Inc., Rockville, MD; 4/24/89) Baygon technical (batch # 0030208, 98.5% state purity); DMSO vehicle (final concentration 10 ul/ml). Triplicate plates seeded with 5 X 105 primary rat hepatocytes from male Fisher 344 rats were exposed for 18-20 hours to 0, 1.5, 5.0, 15, 50, 150, 500, or 1,000 μg/ml in the presence of [^{3}H]-thymidine. Cells were fixed with ethanol-glacial acetic acid and 50 cells/plate were scored for [^{3}H]-thymidine incorporation by autoradiography. Cytotoxicity and precipitation were seen at 500 and 1,000 μg/ml. Treatment-related increases in nuclear grain counts were not seen. Cytotoxicity was evaluated a parallel trial by measuring lactate dehydrogenase release into medium. Positive controls with DMBA were OK. The study is acceptable with <u>no adverse effect</u> (Morris, 02/22/90).

50021-199 092059 "Induction of and effect on UDS by test substance BOQ 5 812 315." (W. Klein , Austrian Research Center Seibersdorf, 10/86; Mobay No. 94969) BOQ 5 812 315, no purity stated, was fed in the diet to female BOR:WISW rats. Two diets were used: Altromin and Basal Diet No. 531. In the first part of the study, rats were fed control diets or 8000 ppm test article for 24 hours or 7 days, 10 females per group. The epithelial cells of the urinary bladders were isolated and put into culture. The cells were incubated with ^{3}H-thymidine for two hours, washed and prepared for autoradiography. In the second part, 6 rats per group were fed control diet or 40, 200 or 1000 ppm propoxur for 7 days. Positive controls were methyl methane sulfonate and o-phenylphenol. Slides were scored for percentage of cells in S phase and for UDS induction. The addendum is a re-evaluation of the slides for the same endpoints. The study did not indicate an induction of UDS but there was an increase in the percentage of cells in S phase with increasing doses. <u>No adverse effect was indicated</u>. The report is unacceptable (no purity, no analysis of diets, no justification for using only females, other deficiencies noted in worksheet.) (Note amendment in vol. 208, below). Gee, 10/24/91.

50021-208 089697 Addendum to 50021-199 092059, above. Addendum by R. Curren, under Mobay reference No. 94969-1. This addendum was considered in review by Gee on 10/24/91.

50021-262 146086 Wang, C. Y., “Study on genotoxicity and mitogenicity of urine of rats fed Baygon”, Michigan Cancer Foundation, 1/26/96. Bayer Report #107163. This was a follow-up to 50021-199 092059, "Induction of and effect on UDS by test substance BOQ 5 812 315." (W. Klein , Austrian Research Center Seibersdorf, 10/86; Mobay No. 94969), which yielded inconclusive findings. Most of the present report addressed method development. Rats were treated under various regimens, then sacrificed, bladders were washed with buffered saline, then incubated with a solution containing trypsin to release epithelial cells, which were evaluated *in vitro*. Investigators did not succeed in a method development for mitogenicity assessment, so only UDS was assayed after propoxur administration. For this, 4 female Wistar rats/group were treated as follows: (1) diet control, (2) 18 days feeding with 0.8% propoxur in diet, or (3) 50

mg/kg of 3,2'-dimethyl-4-aminobiphenyl (DMABP) 4 hr before sacrifice of phenobarbital-primed rats. UDS assay was undertaken in Eagle minimum essential medium containing antibiotics, 1% fetal bovine serum, 10 mM hydroxyurea, and 5 μCi of [^{3}H]thymidine in a 0.25 ml suspension on a coverslip. After incubation, washing, and fixing, the sample was place on a slide, treated for 2 weeks with a photographic emulsion, and counterstained with hematoxylin. UDS evaluation was based on net grain counts (nuclear grains minus grains/similar area of cytoplasm). Apparently 2 replicates, each containing 28 cells, were evaluated per treatment. Propoxur was **negative** for UDS induction under these conditions. DMABP positive control was functional in this assay. Under these conditions, the propoxur dose demonstrated mild to moderate hyperplasia of the bladder epithelium. Useful study, not applicable to guidelines. Aldous, 11/14/97.

50021-019 035648 "Propoxur - Mutagenicity Test on Bacterial Systems". (Nitokuno, Agricultural Chemicals Institute, Report No. 103, 2/24/78, Sponsor no. 65844). Propoxur, 98.0%, with Bacillus subtilis strains NIG17 and NIG45 rec+/- test; tested at 0, 3, 30 or 300 ug/disc, no activation only; no evidence of cytotoxicity - therefore, no test. Unacceptable (no justification of amounts used, no activation, single plate per amount, no cytotoxicity). J. Schreider, 2/21/85.

EPA 1-liner: Acceptable. Not a mutagen.

50021-113 035651 Summary of 35648.

50021-098 026403 "Propoxur, Microbial Mutagenicity Study". (Institute of Environmental Toxicology, 2/28/83, Sponsor no. 84124). Propoxur, 98%; tested with Bacillus subtilis strains H17 and M45 without activation only; applied to 10 mm filter disk at 0, 50, 100, 200, 500, 1000, 2000, 5000 and 10,000 ug/disk; no differential growth and no cytotoxicity = no test; unacceptable (no test, no activation included). J. Schreider, 2/25/85.

50021-098 014188 "Carbamate UN Technical: Pol A_1^- Test on E. coli for Potential DNA Damage". (Bayer AG, 1/6/83, Report No. 11403, Sponsor no. 82739). Carbamate UN technical, 98.5/98/6% (no further identification); tested with Escherichia coli strains (K12)p 3478 ($polA_1^-$) and W 3110 ($polA^+$), with and without rat liver activation; tested at 0, 62.5, 125, 250, 500 and 1000 ug/plate on a filter disk, trial 1, and at 0, 625, 1250, 2500, 5000 and 10,000 ug/plate, trial 2; no evidence of differential growth and no evidence of cytotoxicity (= no test). **Unacceptable.** J. Schreider, 2/25/85.

50021-113 014185 Summary of 014188.

50021-118 026404: This record contains an exact duplicate of the study found at document # 50021-098, record # 014188.

50021-118 026405 "Induction of Gene Conversion in Diploid Yeast by Chemicals: Correlation with Mutagenic Action and Its Relevance in Genotoxicity Screening". Publication: Mutation Research 64: 1-17 (1979), Murthy, M. S. S., author. Sponsor no. 86667. Propoxur was one of over 200 chemicals screened Saccharomyces cerevisiae strain D4. Propoxur was negative. Unacceptable. J. R. Gee, 9/10/85.

50021-113 035652 Summary paragraph of two publications in Mutation Research, 1974, on Saccharomyces cerevisiae to 1000 ppm (4.78 mM) for mitotic gene conversion with negative results.

50021-113 035653 Summary paragraph on 1977 publication in Mutation Research, single-strand break formation in human fibroblasts - negative findings reported.

50021-113 035657 "Propoxur - Mutagenicity Test on Bacterial Systems". (Institute of Environmental Toxicology, Japan, 8/28/79). Propoxur, 98%; tested with Bacillus subtilis strains H17 and M45 for rec in disk assay without activation only; tested at 0, 50, 100, 200, 500, 1000 or 2000 ug/disk; no zone of inhibition at any concentration for either strain; unacceptable - no test. Also, no activation was included. Single value per concentration. J. Schreider, 2/20/85 and J. Gee, 12/29/86.

DNA Damage effects of Propoxur metabolites:

50021-095 014182; "Effect of an Active Ingredient and Three Metabolites on the DNA Metabolism," OEFZS Report no. A050 BL-453/84, Sponsor no. 88582; Austrian Research Centre Seibersdorf GmbH, Vienna, Austria; 3/84; Propoxur (BOQ 5 812 315) and three metabolites (THS 2490, THS 1240, THS 1241b) in 10% ethanol were given po at 10 mg/kg to 24 male Wistar rats / compound. The rats were sacrificed 24 hours later and suspensions of spleen cells were prepared and used to measure programmed DNA synthesis, suppressed programmed DNA synthesis, unprogrammed DNA synthesis, and nucleoid sedimentation. In vitro DNA binding was measured using purified liver DNA. THS 2490 and 1241b decreased programmed DNA synthesis but propoxur and THS 1240 had no effect. No effect of any test article was seen on unprogrammed DNA synthesis, nucleoid sedimentation or DNA binding. No adverse effect indicated. Originally reviewed as unacceptable (not conducted by standard protocol, J. Schreider, 2/22/85) and changed to acceptable (M. Harnois, 6/17/87). Re-review has determined that the study is unacceptable but possibly upgradeable with submission of rationales for: dosing vehicle, dose levels, dose and route of exposure of positive control, use of spleen cells for the in vivo assays, and lack of metabolic activating system for the in vitro binding assay (J. Schreider, 2/22/85, S. Morris, 10/11/88).

EPA 1-liner: Supplementary. Dosage level: 10 mg/kg (by mouth) for all compounds. Two Baygon metabolites (THS 2490 and THS 1241b) had a suppressive effect on programmed DNA synthesis in rat spleen cells; Baygon and THS 1240 had no effect on this parameter. None of the compounds tested had any effect on suppressed program DNA synthesis, DNA repair, or DNA nucleoid sedimentation rates. Binding of test compounds to DNA occurs at low levels, if at all.

50021-095 014176 "Isopropoxyphenol, Test on S. cerevisiae D7 for the Induction of Mitotic Recombination". (Bayer AG, 8/20/84, Report No. 12876, Sponsor no. 88506). Isopropoxyphenol, VK32-806, metabolite of propoxur, no purity stated, tested with Saccharomyces cerevisiae diploid strain D7 for mitotic crossing-over and mitotic gene conversion with and without activation with S9 mix prepared with rat liver; incubated for 16 hours with 0, 625, 1250, 2500, 5000 and 10,000 ug/ml in test 1; at 0, 187.5, 375, 750, 1500 and 3000 ug/ml in test 2 and at 0, 185.9, 260.3, 364.4, 510.2, 714.3 and 1000 ug/ml in trial 3; five plates for mitotic gene conversion and 10 plates for mitotic crossing-over and toxicity; cytotoxic at concentrations greater than 750 ug/ml; no evidence for genotoxic effect in either assay;

acceptable (note that no purity was given and the test was conducted with a metabolite). J. Schreider, 2/21/85.

50021-095 014178 "Brenzcatechin, POL Test on E. coli to Evaluate for Potential DNA Damage". (Bayer AG, 2/29/84, Report No. 12497, Sponsor no. 88508). Brenzcatechin, batch VK 32-800, metabolite of propoxur, no purity stated; Escherichia coli strains (K12)p 3478 (repair deficient) and W 3110 (pol A+) with and without rat liver activation; test article placed on filter disk at 0, 625, 1250, 2500, 5000 or 10,000 (not soluble), trial 1, at 0, 1200, 1800, 2700, 4050 and 6075 in trial 2 and 3 and at 0, 800, 1200, 1800, 2700 and 4050 in trial 4, 4 plates per amount; water for vehicle; no genotoxic effect reported at concentrations which were cytotoxic. Acceptable study on metabolite (no purity given). J. Schreider, 2/22/85.

NEUROTOXICITY, HEN

50021-027 017614 "Histological Studies of Spinal Cord and Sciatic Nerve from Neurotoxicity Tests on Chickens with BAY 39007". (Bayer AG, 7/10/67, Report No. 373, Sponsor no. 20937). Propoxur, no purity stated, fed for 30 days to chickens at 0, 300, 1500, 3000 or 4500 ppm; 3 per group were killed immediately at the end of dosing, 2 -3 after 28-day observation period; evaluated as an invalid study (no positive control, no basis for dose levels, not an appropriate protocol). No effect reported. J. Schreider, 2/19/85.

50021-027 017617 "Neurotoxic Studies with Active Ingredient Boecker 58 12 315". (Bayer AG, 3/3/66, Sponsor no 17974). Propoxur, no purity stated; single oral application of 100, 200, 500 or 1000 mg/kg and observed for 6 weeks or a single ip injection of 25, 37.5, 50 or 100 mg/kg. Some deaths and acute toxicological effects but no noted neurotoxic damage. Eight per group were fed at 0, 300, 1500, 3000 or 4500 ppm for 30 days with no neurotoxic damage reported. Report is incomplete with the figure and table of results missing. Reviewed as invalid. No positive controls, no analysis of dosing material, missing data. J. Schreider, 2/19/85.

EPA 1-liner: Minimum. No evidence of neurotoxic damage found up to 1000 mg/kg given orally in the presence and absence of atropine. No evidence of neurotoxic damage found up to 100 mg/kg given intraperitoneally in the presence and absence of atropine.

NEUROTOXICITY, RAT

**50021-248 133415 Dreist, M. and Popp, A., "BOQ 5812315 (c. n. Propoxur): Acute oral neurotoxicity screening study in rats", Bayer AG, Department of Toxicology, Wuppertal, 9/13/94. Miles Report #106387. Wistar rats (12/sex/group) were dosed once with 0, 2, 10, or 25 mg/kg propoxur (99.4%) by gavage in PEG-400 vehicle. Rats were evaluated in a standard FOB battery and in an automated motor activity monitoring apparatus prior to testing, and at days 0, 7, 14. Six/sex of these controls and high dose rats were given histopathological examinations at day 14. Additional groups of 6/sex/group were killed about 45 min after dosing, for cholinesterase assays. There was no NOEL for some of the FOB measurements on day 0, due to apparent cholinergic effects (such as repetitive chewing in females, and males tending to sit or lie down when the normal behavior is to stand). Brain cholinesterase enzyme inhibition was dose-related at all dose levels, and statistically significant ($p < 0.01$) in both sexes at 2 mg/kg. The NOEL for neurotoxicity other than apparent cholinergic effects was 25 mg/kg. The 1995 DPR review requested additional data to verify analytical capabilities of the test facility, and

sought clarifications about histopathology. Record Nos. 144724 and 144727 address the test facility capabilities. These were reviewed in detail by T. Kellner (Nov. 1997). Record No. 144726 reconciles a noted discrepancy between individual and summary histopathology data. The new information allows an upgrade to **acceptable** status. The latter records are noted in the Summary of Toxicology Data. Aldous, Dec. 1, 1997.

50021-260 144726 Correction of page 372 of Record No. 133415, above, showing that sciatic nerve was examined in all male rats, consistent with individual data in that report. A printing error was not identified in the report as originally prepared (correction copy is inserted into that report). Is clear from the report, as amended, that nearly all protocol tissues were examined in nearly all cases in both sexes, so that the study is acceptable in this respect. Aldous, 11/25/97.

50021-259 144724 Validation studies, some employing known neurotoxic agents, demonstrating the capability of laboratory technicians to reproducibly identify neurotoxic FOB effects, and the capability of the laboratory to assess alterations in motor activity. These validation studies, reviewed by T. Kellner in November of 1997, suffice to allow an upgrade of Record No. 133415 to acceptable status. Aldous, 11/25/97.

** 252, 261; 137937, 144727; “Subchronic Neurotoxicity Screening Study in Wistar Rats (Thirteen-Week Administration in the Diet with a Four-Week Recovery Period)”; (M. Dreist and A. Popp; Bayer AG, Department of Toxicology, D-42096 Wuppertal, Germany; Report No. 106867; 4/4/95); BOQ 5812315 Technical (purity: 99.5%) was administered in the diet at concentrations of 0, 500, 2000 and 8000 ppm to 12 rats/sex/group for 13 weeks ((M): 0, 33, 132, 543 mg/kg/day, (F) 0, 39, 163, 703 mg/kg/day). Two additional groups of 12 animals/sex/group were treated with 0 or 8000 ppm of the test material for 13 weeks and then maintained for a 4 week recovery period. The mean body weights of the animals in the 2000 and 8000 ppm treatment groups were significantly lower than that of the control (wk 13: 2000 ppm (M: 87.7% of control, F: 92.8% of control), 8000 ppm (M: 78.7% of control, F: 79.7% of control). In the Functional Observational Battery (FOB), no effects were noted in the males. For the females, at various time points, grip strength was reduced in the 8000 ppm ($p < 0.05$), but in no consistent manner. Foot splay was, likewise, significantly less in this group at the various time points ($p < 0.05$). During the FOB, handling of the animals apparently precipitated clonic involuntary motor movements in 5 of 24 females of the 8000 ppm group. Slow pupillary reflex was noted in 4 of 24 males and 2 of 24 females in the 8000 ppm group. Brain Cholinesterase activity was affected in a dose-related manner with significant reduction in the 500 (M only, 85.6% of control), 2000 (M: 76.2% of control, F: 81.7% of control) and 8000 ppm groups (M: 72.3% of control, F: 80.6% of control). N-Demethylase and O-demethylase activities were significantly increased in the livers of the 2000 (M only) and 8000 ppm (both). Liver cytochrome P-450 content was likewise significantly greater in the males of the 500 and the 2000 ppm groups and both sexes in the 8000 ppm group. There were no treatment-related lesions evident in the histopathological evaluation. **No adverse effects,** clonic involuntary movements in females at the high dose exceeded the maximum tolerated dose. **NOEL:** (M)<500 ppm (based upon reduced brain cholinesterase activity in the 500 ppm group, < 33 mg/kg/day), (F) 500 ppm (based upon reduced brain cholinesterase activity and lower mean body weights for animals in the 2000 ppm treatment group, 39 mg/kg/day); **Study acceptable.** (Moore, 9/18/97)

50021-261 144727 This record contains historical control data and method validation studies considered in acceptability evaluation of recent acute and subchronic rat neurotoxicity studies. An extensive review of this record was completed by T. Kellner in November of 1997. The

correspondence between observations of different technicians was satisfactory, verifying that the test facility was capable of identifying treatment-related neurotoxic effects. Aldous, 11/25/97.

50021-117 024729: "Neurotoxicologic Studies of Two Carbamate Pesticides in Subacute Animal Experiments," Toxicology and Applied Pharmacology, 27:465-476 (1974). This was a 50-day neurobehavioral study in which rats were exposed to 0, 12.5, and 25 ppm propoxur in the diet. Neurobehavioral effects were observed with a LOEL = 12.5 ppm. Evaluations and worksheets were not done because the study did not conform to a required test type (S. Morris, 10/6/88).

Three additional records were listed in the DPR data record printout for propoxur relating to mammalian neurobehavioral studies: Document Nos. 153-540, 153-546, and 153-547; corresponding to Record Nos. 155835, 155841, and 155842. These studies used propoxur as a positive control substance to validate the capabilities of the Ciba-Geigy laboratory in Farmington, CT to detect neurotoxicity study endpoints. These studies were under the direction of J. C. Pettersen, and were conducted in 1991 to 1992. Several acute effects consistent with cholinesterase inhibition were reported. Since the studies accepted by DPR in late 1997 were performed by different investigators at a later time in a different facility, this set of records does not need to be reviewed to validate the recent propoxur studies. Aldous, 12/3/97.

MISCELLANEOUS STUDIES

50021-098 014186; "BOQ 5812315 (Propoxur, the Active Ingredient of Baygon), Tests for Induction of Liver Microsomal Enzymes;" This study was not evaluated because its did not conform to a required test type.

SUBCHRONIC, RABBIT

50021-183 073664 "BOQ 5812315 (common name: Propoxur) subchronic dermal toxicity study in rabbits". Bayer AG, 3/23/89. NZW rabbit, 10/sex/group at 0, 50, 250, and 1000 mg/kg/day, 5 working days/week, 6 hr exposures/day for 13 weeks. Summary notes that there were no treatment effects at any dosage. No CDFA written review. C. Aldous, 5/2/89.

These records have been evaluated.

50021-019 017607
50021-019 017608
50021-019 035648
50021-027 017610
50021-027 017611
50021-027 017612
50021-027 017613
50021-027 017614
50021-027 017615
50021-027 017616
50021-027 017617
50021-028 017618
50021-028 017619
50021-029 017609
50021-075 026402
50021-088 009592
50021-088 009594
50021-088 009595
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50021-088 009601
50021-088 009602
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50021-098 014192
50021-098 026403
50021-098 035647
50021-106 012245
50021-106 012246
50021-106 025222
50021-113 035652
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50021-134 047933
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